known but would appear to include antirheumatic and anti-inflammatory properties. Specific actions described include the suppression of neutrophil chemotaxis and the enhancement of the function of killer cells. Administering leucovorin calcium can reverse clinical improvement, suggesting folate antagonism as a mechanism. No effect on prostaglandins has been reported.

The use of methotrexate should be considered when more traditional methods of treating rheumatoid arthritis, such as gold therapy, have failed. Although the accumulated data suggest that methotrexate as primary therapy may be recommended in the future, long-term follow-up information is not yet available to support the safety of this approach. Moreover, methotrexate has not yet been proved to induce true remissions in these patients. Severe flares of rheumatoid arthritis after discontinuing therapy have been reported.

Because of the potentially severe side effects, candidates for therapy must be selected carefully and monitored continuously. Contraindications include the presence of infection, hepatic disease, alcohol intake, or reduced renal function as estimated by an age-adjusted creatinine clearance. Relative contraindications include either hematologic abnormalities unrelated to rheumatoid arthritis or interstitial lung disease.

The baseline evaluation should include a complete blood count, blood chemistry values, a urinalysis, and a chest roentgenogram in all patients. Regularly scheduled monthly visits with a physician familiar with the drug and a redetermination of blood count and liver function indexes are prudent. The necessity of doing a liver biopsy is controversial, but most reports suggest a biopsy after a cumulative dose of 1,500 mg. Current practice based on accumulated experience is to do a biopsy only if liver enzyme levels remain elevated after stopping the drug. When evaluating a biopsy specimen, the awareness that pretreatment histologic abnormalities have been reported should be kept in mind. Pulmonary function should be assessed if respiratory symptoms develop because methotrexate toxic effects include interstitial pneumonitis. The initial dose is 7.5 mg one day per week with the maximal dose seldom exceeding 15 mg.

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Thrombolytic Therapy for Acute Myocardial Infarction

ADMINISTERING thrombolytic drugs to patients with acute myocardial infarction results in clot lysis and reperfusion of the occluded coronary artery in about 35% to 75% of patients. Successful reperfusion results in enhanced survival and improved left ventricular function, most likely owing to a decrease in infarct size. Furthermore, a reperfused infarct is less likely to undergo remodeling and expansion, resulting in less deterioration of left ventricular function in the days and weeks after infarction. Most trials have shown that initiating thrombolytic therapy early—within three hours after chest pain begins—improves the success of thrombolysis and survival compared with the results of giving thrombolytic therapy relatively late after the onset of chest pain. The Second International Study of Infarct Survival (ISIS-2) trial, however, showed that intravenous streptokinase therapy lengthened survival, even when given 12 to 24 hours after the start of symptoms. This may have been due to the presence of collateral circulation in certain patients, possibly delaying the time after which irreversible myocardial injury occurred. Alternatively, this may indicate that later reperfusion after a completed infarction may be of benefit by preventing infarct expansion. Many of the initial thrombolytic trials emphasized that the major improvement in survival occurred in patients with anterior myocardial infarctions. A trial from New Zealand, however, and the ISIS-2 trial showed that thrombolytic therapy improved survival rates in patients with inferior myocardial infarctions as well.

The possible benefits of coronary reperfusion in patients with acute myocardial infarctions need to be weighed against the side effects of thrombolytic therapy. The most serious side effect of thrombolytic therapy is intracranial bleeding, which occurs in about 0.5% of patients. Other side effects include bleeding from other sites, hypotension, and reperfusion arrhythmias. Streptokinase also has the potential to cause allergic reactions and, rarely, anaphylaxis. Risk factors that would preclude a patient from receiving thrombolytic therapy include the presence of active internal bleeding, a history of a previous cerebrovascular accident, neurosurgical procedure or head trauma, an intracranial neoplasm, an atrioventricular malformation or aneurysm, and a known bleeding disorder. Investigators have excluded patients older than 75 years from receiving thrombolytic therapy because of a perceived increased risk for intracranial bleeding. The ISIS-2 trial, however, showed no increased risk for intracranial bleeding following intravenous streptokinase therapy in patients older than 75 years. Further studies will be necessary to confirm this observation.

Because thrombolytic therapy fails to lyse coronary thrombi in about 25% of patients, coupled with the observed and perceived risks of coronary reocclusion and reinfarction, many investigators have examined the possible role of adjuvant pharmacologic therapy and mechanical reperfusion in patients receiving thrombolytic therapy. The ISIS-2 trial showed that using aspirin reduced mortality by 21% in patients with suspected myocardial infarctions. This reduced mortality was additive to that due to intravenous streptokinase therapy. Aspirin use also decreased the incidence of reinfarction in patients receiving intravenous streptokinase by approximately 50%. The Thrombolysis in Myocardial Infarction (TIMI) phase IIB trial found that the early administration of metoprolol reduced the incidence of recurrent angina compared with late metoprolol administration, starting on day 6 after an infarction. Furthermore, when given within two hours of the beginning of chest pain, metoprolol therapy reduced the combined incidence of nonfatal reinfarction and mortality. In patients with persistent coronary artery stenosis, coronary angioplasty done immediately after thrombolytic therapy results in increased complications and mortality compared with delayed angioplasty—that is, done one to seven days after an infarction. Furthermore, the TIMI phase IIB trial showed that doing angioplasty one to two days postinfarction failed to improve survival or left ventricular function or to reduce the incidence of reinfarction compared

with conservative management in these patients. Thus, it appears that most patients receiving thrombolytic therapy can be successfully managed without the need for routine coronary angioplasty unless they have symptoms or objective evidence of recurrent ischemia.

At this time there are no definitive data that would show the superiority of one thrombolytic agent over another in terms of improving survival or left ventricular function in patients with acute myocardial infarction. Although the TIMI phase I trial showed that, compared with streptokinase therapy, administering intravenous tissue plasminogen activator achieved a higher incidence of coronary artery patency 90 minutes after it was started, a New Zealand trial failed to show that giving tissue plasminogen activator was better than administering streptokinase in improving overall left ventricular function. It should be noted that both of these trials involved relatively small numbers of patients. Currently there are several large ongoing studies comparing the relative benefit of various thrombolytic agents on survival.

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Reducing Morbidity and Mortality Due to Asthma

DESPITE MAJOR ADVANCES in the understanding of its pathogenesis and the availability of a large number of drugs, morbidity and mortality due to asthma appear to be on the rise. Although the reasons for this disturbing paradox are unclear, there are certain broad treatment guidelines that, if diligently followed, will help to reduce the growing menace of asthma.

Although patients of any age, sex, and race can die of asthma, the disease more frequently ravages socioeconomically handicapped members of the society. In the United States blacks have a higher incidence of death from asthma than whites. Adults older than 65 years and children between the ages of 10 and 14 years are particularly susceptible. Persons with specific immunoglobulin E antibodies to common inhalant allergens are at an increased risk for acute severe attacks of asthma. Most of the patients who die of asthma have a history of severe, poorly controlled disease with poor compliance. Many of these patients also have emotional ailments, particularly depression, isolation, and problems of self-image.

Physicians often fail to realize that there is generally a poor correlation between the symptoms of asthma and the degree of airway obstruction. Patients, on the other hand, commonly develop a tolerance to their symptoms. Thus, there is a failure on the part of both physician and patient to appreciate the severity of bronchial narrowing. Educating patients about recognizing important symptoms and emphasizing the necessity of monitoring airway obstruction by peak flow measurements are the basic steps towards controlling asthma. More often than not, patients can be persuaded to buy a flow meter. Physicians who take care of asthma patients should not only have a peak flow meter on their desk but should also have easy access to a pulmonary function laboratory.

One of the problems related to asthma therapy lies in the way the treatment is delivered to the airways. Although the inhaled route is an effective way of delivering bronchodilators, surveys have shown that more than 50% of patients prescribed an aerosol inhaler used it incorrectly. Furthermore, other studies have revealed that physicians often do a less than satisfactory job of instructing their patients on how to use inhalers. The problem of poor coordination can now be corrected by using spacers and newly developed breath-actuated inhalers. These devices are of particular help in very young and elderly patients who find it hard to use metered-dose inhalers.

Although the treatment of asthma should be tailored to the needs of individual patients, inhaled selective β_2-adrenergic agents constitute the first line of therapy in chronic asthma. When a properly administered β_2-adrenergic drug—including the use of spacers and breath-actuated inhalers—does not provide effective relief of bronchospasm, aerosolized corticosteroids should be prescribed to suppress the airway inflammation that appears to underlie the severe bronchial hyperreactivity of asthma. If used effectively, this combination not only produces maximum improvement in peak flow rates but also cuts down the need for parenteral steroids. Patients who do not respond to the β_2-adrenergic drugs and aerosolized corticosteroids combination deserve a trial of cromolyn sodium. This prophylactic agent is particularly useful for young patients with asthma who are known to have allergies and exercise-induced asthma. Recent studies have found that cromolyn sodium reduces bronchial hyperreactivity in adult patients with asthma as well.

In summary, the rising tide of morbidity and death in asthma can be countered by recognizing high-risk patients, by accurately assessing the severity of airway obstruction, by properly delivering bronchodilators in the airway, and by prescribing cromolyn sodium and corticosteroids judiciously.

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Treatment of Small-Cell Lung Cancer

MANY COMBINATION chemotherapy regimens have activity in patients with small-cell lung cancer. In contrast to the treatment of non-small-cell lung cancer, surgical excision is not generally recommended for patients with small-cell lung cancer because of the propensity for distant spread of the